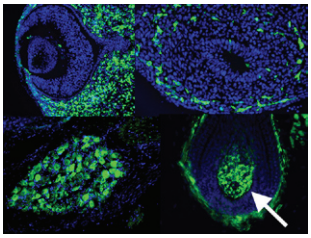
Editors' Notes

Excavating the Origins of Populations and Designations

The identification of multipotential populations in adults is an important, but frequently challenging, avenue of research. In this issue's Review article, Chien and Martin-Puig discuss the latest advances in isolating progenitors with heart cell potential, both resident in cardiac tissue and externally derived. Also in this issue, Shibata et al. from the Okano laboratory report lineage-tracing experiments to look at neural crest-derived cells in embryos and adults. Using two different reporter mice, the authors show that neural crest-derived stem cells (NCSCs) seem to be present at low frequency in the bone marrow of postnatal mice, and in the dorsal root ganglia and whisker pad. Intriguingly, NCSCs are also detected in the same fetal tissues in which hematopoietic stem cells arise and expand. The isolation of stem cells such as these from numerous tissues raise hopes of accessible populations with therapeutic potential, but it remains essential to review these data with a critical eye, and to hold them to high standards before granting the "stem cell" designation. This is perhaps illustrated most clearly by the debate that has occurred regarding the validity and utility of the term "mesenchymal stem cells," or MSCs. With these important questions in mind, the Commentary by Bianco, Robey, and Simmons discusses the history, use, and misuse of the MSC acronym.



HSC Questions Addressed and Readdressed

HSCs are often touted as the "best understood" population of stem cells, and are also considered the most accurately characterized by phenotype. A great deal is known, but three papers in this issue add to the still incomplete picture and underscore just how much more there is to learn. Stem cells are dependent on a balance of intrinsic and extrinsic signals to undergo appropriate cell fate decisions. HSCs have been proposed to respond, in part, to signals delivered by the adhesion molecule N-cadherin. Although an earlier study (Kiel et al., *1*:204) published in *Cell Stem Cell* provided evidence that N-cadherin is dispensable for HSC function, a new report from Linheng Li's laboratory provides evidence that murine HSCs can be divided into "dormant" or "poised" subpopulations based on low-level expression of this surface protein. The cell-cycle status of HSCs, which may differ between the subpopulations described by Haug et al., was also examined in this issue by the Wagers group, who identified a transcription factor that helps maintain a quiescent population of HSCs. When Egr1 is deleted, HSCs actively cycle in the bone marrow and accumulate in the circulation. Remarkably, the blood-borne population maintains functional properties, as assessed in transplant models, and only exhausts after multiple rounds of serial reconstitution. The molecular pathways responsible for this release of quiescence and retention in the marrow are not yet known, but one candidate signaling pathway may be eliminated by the results presented by the Pear group, also in this issue. Using multiple genetic approaches to block all signaling downstream of the canonical Notch cascade, Maillard et al. reveal no apparent requirement for Notch signals in HSC function—even with the enforced expansion imparted by a serial transplantation assay. These findings seem to contrast with earlier gain-of-function studies that implicated Notch signals in the expansion of functional HSCs. Together with the other HSC studies in this issue, these results underscore the difference between what a signal is able to induce and what its requirement is in vivo.

Making Use of Accessible Resources

An important hallmark of the current age of scientific research is the massive accumulation of electronic data. In the stem cell field, the proliferation of expression arrays and related analyses offers an extraordinary opportunity for the growing practice of "data mining." There are potential pitfalls to comparing data generated across analysis platforms and cell types, of course, but new tools are being developed to overcome these hurdles. One such example is described in a paper in this issue from Wong and colleagues. Using a "gene module" analysis technique, the authors identified a core "ESC-like" signature of genes expressed by both murine and human stem cell populations. Remarkably, this same pattern is shared by a variety of human tumors, and induction of this signature in transformed cells parallels the onset of tumorigenicity. The lessons learned from this study not only open doors to better understanding of cancer progression, they also highlight the value of combining data sets across laboratories. In the embryonic stem cell field, multiple approaches are being developed to improve the ability of scientists to share embryonic stem cell lines by developing cell registries and banks. In this issue, the International Stem Cell Forum announces their plan to develop guidelines for a stem cell banking initiative. In addition, a Commentary discusses regulatory issues and other points to consider during the development of centralized ESC banks.